Revision of EPA 1-liners pertaining to the EPA Memorandum (2/14/89) was performed (12/12/89, M. Silva).

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

COUMAPHOS

SB 950-101, Tolerance # 189
Chemical Code # 165

October 28, 1986
Revised 4/20/88, 10/14/88, 8/14/89, 9/19/91, 6/5/92

I. DATA GAP STATUS

COMBINED (Chronic & Onco) RAT: No data gap, No adverse effect.

CHRONIC RAT : No data gap, No adverse effect (see combined, rat)

CHRONIC DOG : Data gap; Inadequate study; Possible adverse effect indicated.

ONCO RAT : (See COMBINED RAT, above)

ONCO MOUSE : Data gap; Inadequate study; No adverse effect indicated.

REPRO MOUSE : Data gap; Inadequate study; Possible adverse effect indicated.

TERATO RAT : No data gap; No adverse effect.

TERATO RABBIT: No data gap; No adverse effect.

GENE MUTATION: No data gap; No adverse effect.

CHROMOSOME: No data gap, Possible adverse effect.

DNA DAMAGE : No data gap; No adverse effect.

NEUROTOXICITY: No data gap; No adverse effect.

----------**Note, Toxicology one-liners are attached**. These pages contain summaries only. Individual worksheets should be reviewed as they may contain additional effects.

** indicates acceptable study

Bold face indicates possible adverse effect

File name T920605

Tox summary updated 8/89, M. Silva, 9/91 by Gee and 6/5/92, Kellner.

Rectified through: Document #: 060, Record #: 113795

Some references to duplicate reports have been omitted.

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. SUMMARY OF TOXICOLOGY DATA

COMBINED RAT :

** 055-056 071101 & 071554 "Studies on Chronic Toxicity and Carcinogenicity in Wistar Rats (Administration with Feed for 24 Months)," (Bayer AG, 9/8/88). Coumaphos technical (batch 100585-001-V, 99.2% pure) was used on SPF Wistar rats (Bor: WISW (SPF Cpb)) at 0 (vehicle = 1% peanut oil), 1, 5 and 25 ppm (50/sex/group for 24 months and 20/sex/group for 12 months). **No adverse effect.** NOEL = 5 ppm (inhibition of plasma and erythrocyte cholinesterase in both sexes). No oncogenic effects were observed with coumaphos. **Acceptable.** M. Silva, 8/4/89.

049 044523 The letter of 5/12/86 from Urban A. Wessling, Regulatory Affairs Administrator of Mobay Corporation states that a combined chronic feeding/oncogenicity study in rats should be completed in September, 1988 and made available to CDFA. Preliminary data are presented in 052 067429. The completed study was received and evaluated (055-056, 071101 & 071554)

052 067429 "Chronic/Oncogenicity in Rats, Status Report After 24 Months," (Bayer Ag, 1987). Coumaphos technical (purity and grade not indicated) were fed to rats (strain not indicated) at 0, 1, 5 and 25 ppm for 104 weeks. At 1 ppm, no signs of toxicity were detected. At 25 ppm, plasma and/or erythrocyte cholinesterase activity was depressed in both sexes. Depression of body-weight and food/water consumption were seen in females at 5 or 25 ppm. In males at 25 ppm, the incidence of small follicles and follicular-cell hyperplasia in thyroids was increased. **This report was a very brief summary and will be considered supplementary information.** M. Silva, 10/11/88.

CHRONIC RAT :

028 909394 & 909396 "Chronic Toxicity of Co-Ral (Bayer 21/99) Fed to Rats for a Period of Two Years." (Dept. of Pharmacology, University of Chicago, 9/21/59 & 9/22/60). 25 Sprague-Dawley rats/sex/dose fed coumaphos at 0, 5, 10, 25, 100 ppm. Changes in kidneys, liver, heart, and lungs at 100 ppm. Decreased cholinesterase and decreased life span. NOEL = 5 to 10 ppm. Too few animals; no hematology, urinalysis, or eye examinations; incomplete histopathology; missing individual data. Incomplete Unacceptable. Remsen(Gee), 4/9/85.
EPA 1-liner: Core Supplementary.

-044 26980 and -028 35743 duplicate of 028 909394 & 909396.

-006 52051, 52052 is "Coumaphos Two-Year Rat Study Interim report after 12 months" (see complete review above).

-042 24628 Porter, M. et al. "Subchronic (13 week) Oral Toxicity Evaluation of Coumaphos in the Rat" (Bayvet [Mobay] Report No. 72586, 2/17/83). Coumaphos technical (Batch R81-154-84) was administered in the feed to 20 Sprague-Dawley rats/sex/dose at concentrations of 0, 2.5 or 10 ppm for 13 weeks. Plasma and RBC ChE was significantly inhibited in both of the groups receiving coumaphos (no effect on brain ChE). No gross, microscopic or behavioral indications of toxicity. No worksheet. Kellner, 6/9/92.

CHRONIC DOG :

028 909394 & 909380 "Chronic Toxicity of Co-Ral Red to Dogs for One Year." (Dept. of Pharmacology, University of Chicago, 9/21/59 & 2/8/60). 2 Beagle dogs/sex/group fed coumaphos at 0, 2, 10, 50 ppm. Decreased cholinesterase levels and hyperplasia of mucosal epithelium in the digestive system. NOEL = 2 ppm. Too few animals; no urinalysis or eye examinations; incomplete histopathology; missing individual data. Incomplete Unacceptable. Remsen(Gee), 4-9-85.
EPA 1-liner: Core Supplementary.

In a rebuttal letter submitted by Mobay Corporation, August 28, 1987, it was stated that a new chronic, dog study will be sent when available (no record#).

055 In a rebuttal letter submitted by Mobay Corporation November 1, 1988, it was stated that the effort to repeat the chronic dog study has been discontinued.

059 98271 "Proposed dose levels for a study of coumaphos in dogs." (Mobay, 8/91) One page of text and several graphs of results of cholinesterase activity on days 0, 13, 27 and 41 following feeding of coumaphos. The data are presented as justification for dose selection for a one-year study. Doses used were 0, 2, 20 and 60 ppm. Day 42 activity of brain cholinesterase was inhibited 11% in both males and females at 60 ppm. No worksheet. Gee, 9/19/91.

ONCOGENICITY RAT :

See above: COMBINED RAT (055-056 071101 & 071554) for an acceptable oncogenicity study.

049 044525 "Bioassay of Coumaphos for Possible Carcinogenicity." (Gulf South Research Institute, 1978). Coumaphos; 0, 10, 20 ppm in feed. No adverse effect. NOEL >20 ppm. Only 2 dose levels and high dose barely toxic; only 25/sex for controls; deficient in blood smears, histopathology, body weights, necropsies. Missing individual data and GLP statement. Incomplete Unacceptable. Kahn and Davis, 10/28/86.
EPA 1-liner: Core Minimum.

ONCOGENICITY MOUSE :

049 044526 "Bioassay of Coumaphos for Possible Carcinogenicity." (Gulf South Research Institute, 1978). Coumaphos; 0, 10, 20 ppm in feed. No adverse effect. NOEL >20 ppm. Only 2 dose levels and high dose not toxic; only 25/sex for controls; deficient in blood smears,

histopathology, body weights, necropsies. Missing individual data and GLP statement. Incomplete Unacceptable. Kahn and Davis, 10/28/86.
EPA 1-liner: Core Minimum.

-040 909398, 44495 are duplicates of 044526.

058 096989 [title of proposed study] "Technical grade Coumaphos (CO-RAL*): An eight-week subchronic cholinesterase study in CD-1 mice". Prospective test facility: Mobay Corp. (Stilwell, Kansas). Registrants proposed at a meeting with CDFA that registrants would undertake an 8-week mouse dietary study, with the purpose of determining whether the dose levels in the 1978 Gulf South Research Institute study (049:044526) were acceptable with respect to an MTD. This record describes the protocol. Reviewed by Aldous, 5/29/91 with comments provided to the registrant. Gee, 9/19/91. This study has been submitted to DPR and a supplemental worksheet has been completed (one-liner is shown below).

189-060 113795 Christenson, W. "Technical Grade Coumaphos (CO-RAL*): An Eight-Week Cholinesterase Study in CD-1 Mice" (Miles Inc., Miles Report No. 74306, 3/31/92). Coumaphos technical (lot 218674L, purity of 98.5%) was administered in the feed to 30 CD-1 mice/sex/dose for up to 57 days at nominal concentrations of 0, 20, 60, 120 and 180 ppm in order to establish an MTD for the animal; specifically, the stated goal was to confirm that a 20 ppm high dose used in a previous chronic study (Miles Report No. 71080) constituted an MTD. No compound-related effects on body weight gain, food consumption, clinical signs, hematologic parameters, or organ weights were reported. Treatment related depressions of RBC and plasma cholinesterase (ChE) were seen at all dose levels (no significant brain ChE inhibition). An MTD was established by the author at 20 ppm "based on the criteria outlined by the Environmental Protection Agency requiring significant depression in a least two cholinesterase measurements". DPR disagrees, based on a lack of brain ChE inhibition, associated cholinergic symptoms or any other clinical sign at doses up to 180 ppm. Supplementary to study -049 044526. Kellner and Gee, 6/2/92.

REPRODUCTION MOUSE :

017 909403 & 909391 "Effect of Co-Ral in the Diet on the Reproduction of Mice." (Dept. of Pharmacology, University of Chicago, 11/13/62). 16 pregnant females fed 10 ppm coumaphos, 20 fed 25 ppm, 5 fed 100 ppm. Mortality at 100 ppm; no 2nd or 3rd generation. Decreased litter size and postnatal deaths. NOEL = 25 ppm. 100 ppm too high; too few animals; no dosing prior to mating; inadequate necropsy and tissue preservation; missing individual data. Incomplete Unacceptable. Remsen(Gee), 4/10/85.
EPA 1-liner: Core Supplementary.

REPRODUCTION RAT :

No study on file.

REPRODUCTION DOGS AND GUINEA PIGS :

017 909403 (Dept. of Pharmacology, University of Chicago, 11/13/62). One paragraph discussion of 12 pregnant guinea pigs and 2 pregnant dogs exposed to 25 ppm coumaphos. Probably the same study as Record #909399 (terato guinea pig) below. Possible reproductive toxicity. Incomplete Unacceptable. Remsen(Gee), 4/10/85.

TERATOGENICITY RAT :

** 049 044524 "Study of the Toxicity of Coumaphos: III. Teratology Study in the Rat." (Miles Laboratories, Inc., 9/14/83). Coumaphos; 0, 1, 5, 25 mg/kg; 28 Females/group; Given by gavage on days 6 through 15 of gestation; Maternal toxicity (tremors) NOEL = 5 mg/kg; Developmental Toxicity >25 mg/kg. No adverse effect. Acceptable. Kahn and Davis, 10/27/86.

EPA ONE-LINER--CORE Grade Minimum. Teratogenic NOEL >25 mg/kg/day (HDT); Fetotoxic NOEL >25 mg/kg/day (HDT); Maternal NOEL = 5 mg/kg/day; Maternal LEL = 25 mg/kg/day (HDT) (Cholinergic effects) Doses tested 1, 5, 25 mg/kg/day by gavage to COBS CD rats.

TERATOGENICITY RABBIT :

** 043 026979 "Study of the Toxicity of Coumaphos: II. Teratology Study in the Rabbit." (Miles Labs, 3/25/83). 17 American Dutch rabbits/dose exposed to 0, 0.25, 2, 18 mg/kg coumaphos. Maternal toxicity (tremors, reduced body weight gain) NOEL = 2 mg/kg. Developmental toxicity >18 mg/kg. No adverse effect. Acceptable. Remsen(Gee), 9/5/86. EPA ONE-LINER--CORE Grade Minimum. Teratogenic NOEL >18 mg/kg/day (HDT); Fetotoxic NOEL >18 mg/kg/day (HDT); Maternal NOEL = 2 mg/kg/day; Maternal LEL = 18 mg/kg/day (HDT) (death 2/17, cholinergic effects) Doses tested 0.25, 2.0, 18 mg/kg/day by gavage in American Dutch rabbits.

TERATOGENICITY GUINEA PIG :

017 909399 "Effect of Co-Ral in the Diet on the Pre-and Post-Natal Development of Guinea Pigs." (University of Chicago, 1/8/66). 16 mated females exposed by feeding to 25 ppm coumaphos; 8 control females. Insufficient information for assessment. Not a recommended species; only one dose; no exposure before mating. Incomplete Unacceptable. Remsen(Gee), 4/10/85.

GENE MUTATION :

** 050 061611 "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)," (Microbiological Associates Study No. T5350.501, Mobay No. 73576, 4/27/87). Coumaphos technical, lot R0703616, 98.9%, was plated with S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 at 667, 1000, 3333, 6667, and 10,000 ug/plate with and without S-9

activation. Each concentration was plated in triplicate. No increase in reversion frequency was observed. Acceptable. Shimer, 1/19/88. M. Silva, 2/16/88.

045 026982 "Asuntol Salmonella/Microsome Test to Investigate the Point-Mutagenic Effect." (Bayer, Institute for Toxicology, 9/10/81). Ames Salmonella test. Strains TA98, TA100, TA1535, TA1537 treated with 20, 100, 500, 2500, 12,500 ug/slide. Insufficient information to evaluate mutagenicity. TA98 and TA100 repeated without confirmation of a mutagenic effect in 0-1000 range. No -S9 control; individual "slide" counts not included; not clear if 2 plates used per dose; test agent needs clarification. Incomplete Unacceptable. Remsen(Gee), 9/5/85.

045 026981 is a duplicate of -045 026982.

CHROMOSOME MUTATION :

**** 057 096793** "Micronucleus Cytogenetic Assay for Coumaphos in Mice" (D. L. Putman, Microbiological Associates, Mobay No. 74161, 2/7/91) Coumaphos technical, 98.0%, lot no. 218674L, was given as a single dose to 15 or 20/sex/group by oral gavage at 0 (1% carboxymethylcellulose), 480, 960 or 1920 mg/kg body weight. At 960 and 1920 mg/kg, mortality was high so only the 480 mg/kg dose was evaluated. Five/sex/group were sacrificed at 24, 48 and 72 hours after dosing. One thousand polychromatic erythrocytes per animal were scored for micronuclei. The proportion of PCE’s per total erythrocytes was also determined but was not affected. Cyclophosphamide was the positive control. At 48 hours in males at 480 mg/kg body weight, the incidence of micronuclei in PCE’s (10/5000 in test group versus 2/5000 in controls) was statistically significant by Fisher’s Exact Test and Student t-test. The study is Acceptable with a possible adverse effect on chromosomes. Gee, 9/19/91.

045 026985, 026986 "Coumaphos, Active Agent of Asuntol Micronucleus Test in Mice to Test Mutagenic Effects." (Bayer Pharmaceutical Division, 10/9/82). Mouse micronucleus assay. 15 of each sex exposed to 15 mg/kg coumaphos by gavage with sacrifices at 24, 48, 72 hours. Mutagenicity cannot be evaluated because there was no indication of toxicity; MTD may not have been used. Incomplete Unacceptable. Remsen(Gee), 9/5/85.

EPA 1-liner--Downgraded to unacceptable 2/14/89. Negative at 15 mg/kg p.o. males & females (only dose tested).

DNA DAMAGE :

** 051 064851 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes with Coumaphos," (Microbiological Associates, laboratory study number T5350.380, Mobay No. 73675, 7/27/87). Coumaphos technical, lot R0703616, 98.9% was tested for unscheduled DNA synthesis in primary rat hepatocytes from male Sprague-Dawley rats cultured in serum-free media at 0.2, 0.6, 2.0, 6.0 or 20 ug/ml. Negative controls were: 1) Williams media E (containing serum) and 2) DMSO (10ul/ml). 7,12-Dimethylbenzanthracene (3 and 10 ug/ml) was used as a positive control. Each concentration was plated in triplicate and 25 cells/culture were counted. None of the coumaphos-treated cells registered unscheduled DNA synthesis. Acceptable. D. Shimer, 1/19/88. M. Silva, 2/22/88.

045 026984 "Asuntol Pol Al Test on Escherichia coli to Investigate DNA-Damaging Effects." (Bayer, Institute for Toxicology, 4/5/83). E. coli strains p3478 (repair deficient) and W3110 (repair proficient) treated with technical coumaphos (99.5%) at 62.5, 125, 250, 500, 1000 ug/"slide". DNA damage cannot be evaluated because of insufficient information. No toxicity noted; protocol not sufficiently explained. Incomplete Unacceptable. Remsen(Gee), 9/5/85.

045 026983 is a duplicate of 026984.

NEUROTOXICITY:

** 039 909369 "Acute Delayed Neurotoxicity of Coumaphos in Hens." (College of Vet. Med., Kansas State Univ., 9/16/81) 15 White Leghorn hens dosed with 22.7 mg/kg coumaphos. No adverse effect. Acceptable. Remsen(Gee), 4/10/85.

-047 26990 is a duplicate of -039 909369.